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The vomiting reflex and the role of 5-HT_3 receptors

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The physiology of the vomiting reflex

The function of emesis

Emesis is fundamentally a protective mechanism to rid the body of ingested poisons and toxins before dangerous amounts have been absorbed. However, emesis may also occur in situations where it seems to be an inappropriate response. For example, emesis can be induced during pregnancy, motion, anxiety or shock and following surgical operations or cytotoxic treatment. In these cases nausea and emesis can adversely affect patients' well-being.

The vomiting reflex

The typical vomiting response is normally the same irrespective of the cause of emesis. The reflex can be divided into pre-ejection and ejection phases. The pre-ejection phase is characterized by nausea which can continue for hours or even days. The function of nausea is unknown, although it is likely that it prevents the further ingestion of poisonous or toxic material and produces an aversive reaction to such material. However, nausea does not necessarily culminate in vomiting but changes can occur in the gastrointestinal tract which frequently lead to vomiting. There is a relaxation of the proximal stomach mediated by vagal efferent nerves, which contains any contaminated food or poisons to the stomach. This relaxation is followed by a contraction, also mediated by the vagus nerve, which starts in the small intestine and propagates in a retrograde direction towards the stomach, returning toxic material to the stomach, ready for ejection. These gastrointestinal changes are not essential for vomiting to occur, as emesis can still occur following vagotomy. The ejection phase is under the control of the somatic nervous system and consists of retching and vomiting. During retching the external intercostal muscles, diaphragm and abdominal muscles contract together, with the glottis closed, causing rhythmic decreases in intrathoracic pressure and simultaneous increases in intra-abdominal pressure. The function of retching is unknown, although it has been suggested that the process may move the contents of the stomach into position before expulsion. Vomiting is achieved by the sudden forceful contraction of respiratory muscles at the same time as relaxation of the upper oesophageal sphincter and opening of the glottis and mouth. The major force for the expulsion of the gastric contents is the contraction of the *rectus abdominis* and the external oblique muscles which compress the stomach. Increased salivation also occurs during vomiting, presumably to provide an alkaline buffer for stomach acid. Emesis is often accompanied by pallor and sweating and vomiting is usually followed by a period of pronounced muscular weakness and lethargy.

The neurophysiology of emesis

The initiation and co-ordination of the vomiting response is carried out by a region of the brain stem often referred to as the vomiting centre. The concept of a discrete area of the brain stem co-ordinating the typical vomiting response was proposed in the 1950s by Wang and Borison.[1–3] However, there does not appear to be a specific localized area of the brain stem from which the vomiting response can be elicited,[4] but it has been suggested that neurones within the nucleus tractus solitarius (NTS) act as a 'central pattern generator' to co-ordinate the sequence of events associated with emesis.[5,6] It may be more appropriate to view the central integration of the vomiting response as mediated via a brain stem vomiting system which includes parts of the NTS, the dorsal motor nucleus of the vagus nerve (DMVN) and the area postrema (AP) (Figure 1).

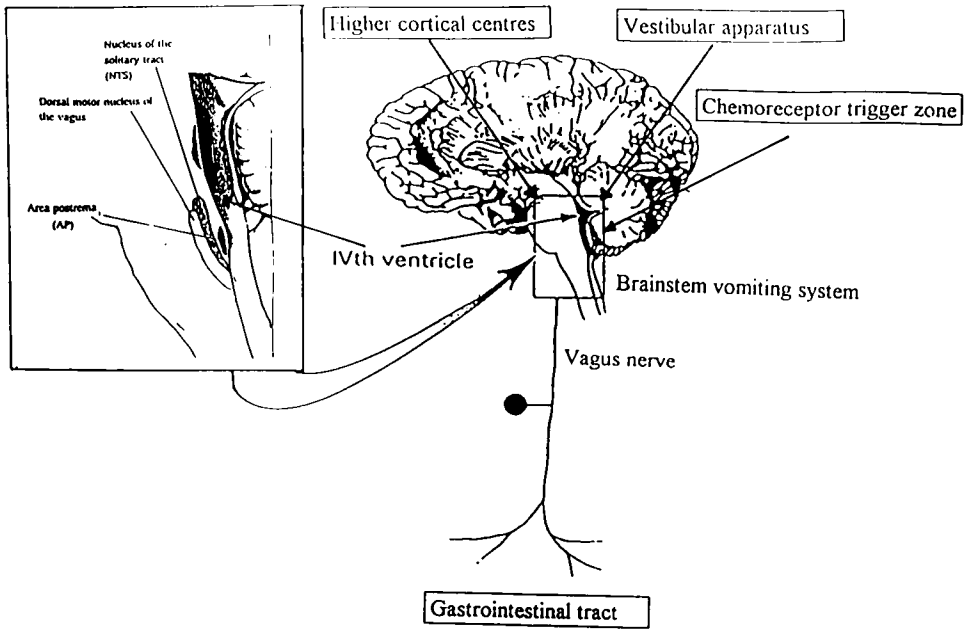

Figure 1. Inputs into the brain stem vomiting system.

The dorsal and ventral respiratory nuclei are also involved in the co-ordination of respiratory and abdominal muscles. Although autonomic fibres do innervate the abdominal visceral structures involved in the emetic reflex, the major components responsible for the expulsion of gastric contents are somatic rather than autonomic. Indeed, the ventral horn of the spinal cord contains neurones responsible for activating the somatic muscles that help expel the gastric contents.

The brain stem vomiting system receives inputs from different areas (Figure 1). There are inputs from higher cortical areas, which is presumably why some people experience emesis in response to emotional stimuli such as terror. This neural pathway may be via the hypothalamus. There are connections between the AP and parabrachical nuclei in the pontine region that are directly connected to the hypothalamus, which in turn receives cortical inputs. This may explain how the feelings of nausea are relayed to the cerebral cortex. Inputs from the limbic system can establish a conditioned response in some cancer patients in whom cues such as the sight of the hospital or the thought of treatment can trigger emesis. It may be that these higher inputs have a role in modulating the sensitivity of the emetic reflex. There are also inputs to the vomiting system from the vestibular apparatus which explains why some people are prone to motion sickness. Indeed, the vestibular labyrinth system is essential for motion-induced emesis. An emesis 'detector' is also located in the AP, the chemoreceptor trigger zone.[1,3] The microvasculature of the AP does not have endothelial occluding junctions and therefore lies outside the blood-brain barrier. In addition, there are no extracellular occluding junctions between cells that overlie the AP.[7] The AP is therefore in contact with both the CSF and blood and from an anatomical point of view is in an ideal position to detect the presence of toxins in either fluid. Another important 'detector' of the requirement to vomit is the gastrointestinal tract. There are mechano-receptors, located in the wall of the gut, sensitive to over distension or increased motility, and chemoreceptors, located in the wall of the upper gut, sensitive to toxins and poisons. The venous effluent of the stomach and duodenum passes to the liver via the hepatic portal vein, making it possible that vagal afferents innervating the liver could also be activated by chemicals and toxins. Once activated, these receptors relay information, largely via the vagus nerve (which contains 80–90% of afferent fibres), to the brain stem vomiting system. The afferent fibres of the vagus nerve project to the AP and NTS. A large proportion of these afferent nerves terminate in a region of the NTS called the subnucleus gelatinosus (or area subprostrema).[8,9] A number of different receptors and neurotransmitters have been implicated in the vomiting reflex. Many of these have been found in the brain stem vomiting system. This

review focuses on the role of 5-HT and 5-HT$_3$ receptors in the vomiting reflex.

5-hydroxytryptamine (5-HT)

5-HT is an indole amine produced from the dietary amino acid tryptophan. It has been known to physiologists since the beginning of the century and occurs widely in plants and animals. It is found in mammals, birds, reptiles, amphibians and molluscs, and in plants such as pineapple, banana and nettles. It was first recognized as a vasoconstrictor substance in serum which confounded attempts to perfuse isolated organs with blood. In 1948 it was isolated and identified chemically.[10] Subsequently, it was found to occur in blood platelets, in the enterochromaffin cells of the gut and in neurones. The physiological effects of 5-HT baffled scientists for many years. Its actions varied between species and were often dependent on the experimental conditions.

5-HT receptor classification

Research carried out by a number of groups showed that the different actions of 5-HT were mediated via a variety of different receptors. This was formalized into a receptor classification in 1986, and this has recently been updated.[11] This classification describes four receptors for 5-HT (5-HT$_1$, 5-HT$_2$, 5-HT$_3$ and 5-HT$_4$) with additional 5-HT$_1$ and 5-HT$_2$ receptor subtypes. No subtypes of the 5-HT$_3$ or 5-HT$_4$ receptor have been identified. However, it is recognized that there are differences in the 5-HT$_3$ receptor between species.[11,12] Several new 5-HT receptors have recently been cloned and named 5-HT$_5$, 5-HT$_6$ and 5-HT$_7$ but they have yet to be fully characterized *in vivo*.[11] The 5-HT$_3$ receptor is unique amongst all these 5-HT receptors in being the only receptor that forms part of a ligand-gated cation channel.

5-HT$_3$ receptor antagonists as anti-emetics

The first selective 5-HT$_3$ receptor antagonist, MDL 72222, was described in 1984.[13] Subsequently, a number of 5-HT$_3$ receptor antagonists have been reported in the literature. Interest in the therapeutic potential of 5-HT$_3$ receptor antagonists as anti-emetics was generated by two findings. Firstly, in 1978, it was shown that metoclopramide, which was used as an anti-emetic and is a selective dopamine receptor antagonist, also had significant activity at the 5-HT M receptor (now referred to as the 5-HT$_3$ receptor).[14] Secondly, independent research groups at Glaxo and Sandoz, both in collaboration with Bradford University, and at Beecham, established that 5-HT$_3$ receptor antagonists inhibited chemotherapy-induced emesis in ferrets.[15-19] These compounds are considerably more potent than metoclopramide in this model and did not cause any overt side-effects unlike metoclopramide, which caused sedation even at doses which inhibited emesis by only 50%. This offered the possibility that selective 5-HT$_3$ receptor antagonists would be anti-emetic in patients without inducing the distressing extrapyramidal reactions often associated with dopamine receptor antagonists such as metoclopramide. Initially, 5-HT$_3$ receptor antagonists were investigated in the clinic against emesis induced by chemotherapy, as this is often extremely severe. Indeed, ondansetron, the first highly selective 5-HT$_3$ receptor antagonist to be developed and marketed, is extremely effective against emesis induced by chemotherapy or radiotherapy in cancer patients and is a major advance in the management of these patients.[20] Recent studies show that ondansetron is also effective against emesis that occurs following surgery.[21]

Distribution of 5-HT$_3$ receptors

5-HT$_3$ receptors are densely located in areas known to be involved in the emetic reflex. Thus there are 5-HT$_3$ receptors on vagal afferent terminals[22,23] which innervate the gastrointestinal mucosa, and on the vagal afferent nerves located in the brain stem vomiting system (*ie* the DMVN, the NTS and the AP).[24-26]

Chemotherapy- and radiotherapy-induced emesis

Peripheral mechanisms

Large quantities of 5-HT (about 80% of the body's total 5-HT content) are contained in the enterochromaffin cells located close to vagal afferent terminals in the gastrointestinal mucosa. Evidence suggests that cancer chemotherapeutic drugs or radiation cause the release of 5-HT from these cells. Gunning *et al.*[27] found cisplatin-induced damage and in-

flammation of the ferret gastrointestinal tract was accompanied by an almost two-fold increase in the content of 5-HT and its metabolite 5-hydroxyindolacetic acid (5-HIAA) in the ileal mucosa. Since there was no change in noradrenaline levels in the same tissue, it is unlikely that the change in 5-HT was caused by generalized tissue damage. Furthermore, Barnes *et al.*[28] found that cisplatin-induced emesis in ferrets could be prevented by pretreating the animals with chlorophenylalanine, an inhibitor of 5-HT synthesis. A clinical study by Cubeddu *et al.*[29] has provided supportive evidence for the role of 5-HT in chemotherapy-induced emesis. In this study the urinary output of 5-HIAA was measured in patients receiving cisplatin chemotherapy together with either ondansetron or placebo. In patients given placebo, the rise in urinary 5-HIAA correlated with the onset and development of emesis. The amount of urinary 5-HIAA produced by patients in this study can only be accounted for by release of 5-HT from enterochromaffin cells. Moreover, similarity between the urinary 5-HIAA levels in the placebo and ondansetron groups suggests that 5-HT_3 receptor antagonists do not affect the release or metabolism of 5-HT but antagonize its action on vagal afferent neurones. Indeed, these findings have been repeated with the highly emetogenic cytotoxic agent dacarbazine.[30] Interestingly, cyclophosphamide and low dose cisplatin (two cytotoxic agents that induce less severe emesis than high-dose cisplatin and dacarbazine) produce small and inconsistent increases in urinary 5-HIAA levels. These findings suggest that the amount and time course of 5-HT release determine the severity, time of onset and the pattern of emesis produced by a specific anti-cancer drug .[30]

Central mechanisms

The importance of central 5-HT_3 receptors in emesis has been demonstrated in ferrets. Low doses of ondansetron or MDL72222 injected directly into the AP caused a dose-related inhibition of vomiting and retching.[31] Furthermore, it has been shown that central administration of cisplatin induces emesis in cats which is inhibited by the intracerebroventricular injection of the 5-HT_3 receptor antagonist zacopride.[32] However, the source of 5-HT which activates these central receptors is not known. It is unlikely that 5-HT released from the enterochromaffin cells reaches the vomiting system via the plasma, as 5-HT is rapidly metabolized. The ventral surface of the AP has neurons which contain 5-HT.[33] It is therefore possible that a direct action of cytotoxic drugs or even activation of vagal afferent nerves causes 5-HT to be released from these neurones. The released 5-HT could then activate 5-HT_3 receptors located presynaptically on terminals of the vagus nerve within the vomiting system. It has also been suggested that an endogenous emetic factor may be released from the gastrointestinal tract and stimulate the AP via the blood. One proposed candidate for this factor is the neuropeptide PPY. Indeed, emesis induced by the closely related neuropeptide NPY is blocked by the 5-HT_3 receptor antagonist zacopride.[34]

Peripheral and central mechanisms of action

The abolition of chemotherapy-induced emesis in ferrets following abdominal vagotomy[35] suggests that chemotherapeutic drugs have a peripheral site of action which is of primary importance. However, Pratt and Bowery[36] have shown that after bilateral or unilateral vagotomy above the nodose ganglion in ferrets there is a decrease in the number of 5-HT_3 binding sites in the brain stem. Therefore, not only is the peripheral input to the vomiting system prevented by vagotomy, but also any possible role for central 5-HT_3 receptors is reduced. Interestingly, in this context, the injection of the 5-HT_3 agonist, 2-methyl 5-HT, into the AP of non-vagotomized ferrets does not induce emesis.[31] An explanation for these observations is that 5-HT acts both centrally and peripherally in a synergistic manner so that activation of 5-HT_3 receptors at both sites is necessary to induce emesis. However, antagonism of 5-HT_3 receptors at one or both of these sites prevents emesis. The effectiveness of a single intravenous dose of ondansetron in the prevention of cisplatin-induced emesis over the first 24 h following treatment[37] suggests that inhibition of the initiation of the emetic reflex is adequate for control of acute emesis following cisplatin.

Post-operative nausea and vomiting (PONV)

This review has focused on the role of 5-HT and 5-HT_3 receptors in mediating emesis induced by cytotoxic drugs and radiation. However, it has been shown that ondansetron is effective in ameliorating

nausea and vomiting which may occur following surgical operations involving general anesthesia.[21] Little is known about the mechanisms of PONV, as unlike chemotherapy-induced emesis there are no animal models that can be studied. However it may be profitable to speculate on how the emetic reflex may be activated and the role of 5-HT$_3$ receptors.

Peripheral mechanisms

Several surgical procedures may release 5-HT from the enterochromaffin cells and induce emesis via a mechanism similar to that outlined above. The anaesthetic itself could disrupt enterochromaffin cells and induce the release of 5-HT. A similar mechanism of cell disruption may also occur following gastrointestinal distension caused by diffusion of nitrous oxide into the lumen of the gastrointestinal tract.[40] In addition, laparotomy, involving manipulation and irritation of the gastrointestinal tract could activate vagal afferents via 5-HT release. Vagal afferents from other abdominal and thoracic systems, namely the heart and respiratory tract, also terminate in the brain stem vomiting system.[41] Thus cardiovascular and respiratory perturbations such as hypertension and hypoxia associated with surgery and anaesthesia may sensitize the vomiting system through neuronal pathways involving 5-HT. However, endogenous 5-HT and 5-HT$_3$ receptors are not involved directly in the control of cardiovascular or respiratory function as ondansetron has no effect on these systems.[42] Patients undergoing surgery to the head and neck region are particularly susceptible to PONV.[40] In this context it is known that sensory afferent fibres of the trigeminal nerve terminate in the NTS[43] and 5-HT$_3$ receptors are present in the spinal trigeminal nerve complex[44] which may have a role in inducing or sensitizing the vomiting system.

Central mechanisms

Anaesthetic substances in the blood, CSF or both, could stimulate neurones within the AP (the site of the chemoreceptor trigger zone for emesis) and activate the vomiting reflex via a 5-HT pathway. Similarly the anaesthetic could affect the vomiting reflex via 5-HT-containing neurones, or inter-neurones, in the NTS . Pain in the postoperative period may also predispose patients to PONV. Painful stimuli from the viscera are transmitted to the CNS via the splanchnic nerves. In this context it is interesting to note that sectioning of the splanchnic nerves in the ferret, while having no effect itself on the emetic response to cisplatin, enhanced the anti-emetic effect of vagotomy.[45] Thus it is likely that painful stimuli induce discharge of splanchnic afferent nerves which in turn contribute to the initiation of the vomiting reflex. As ondansetron completely blocks the emetic response to cisplatin in the ferret it is possible that 5-HT$_3$ receptors are involved in the splanchnic component of the vomiting reflex.

Conclusions

5-HT$_3$ receptors are densely located in areas known to be involved in the emetic reflex, *ie* vagal afferent terminals which innervate the gastrointestinal mucosa and the vagal afferent nerves located in the brain stem vomiting system. The importance of these receptors in mediating emetic responses to cytotoxic drugs, radiation and surgery/anaesthesia has been demonstrated by the anti-emetic effect of the highly selective 5-HT$_3$ receptor antagonist ondansetron. There may be other emetic stimuli which induce emesis via a 5-HT$_3$ receptor mechanism. Indeed, a recent study shows that ondansetron is effective against emesis induced by co-trimoxazole administration to AIDS patients.[46]

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